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Autism Spectrum Disorder: Sniffing Out a New Biomarker

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Early intervention improves prognosis in autism spectrum disorder, yet diagnosis is very difficult in preverbal children. A new study demonstrates that the automatic adjustments in sniffing patterns to pleasant and unpleasant odors may provide a window into early diagnosis.

Autism spectrum disorder (ASD) is widely recognized as a neurodevelopmental condition characterized by early emerging and persistent deficits in social communication and social interaction, often combined with restricted, repetitive patterns of behaviors, interests, and activities [1]. Despite extensive research and clinical efforts, ASD remains exceedingly difficult to diagnose before age two —most children are diagnosed at 5–6 years of age. This is a critical limitation because early treatment is associated with a better prognosis [2]. As such, there is a profound need for more sophisticated and quantifiable biological markers that appear early in development and that could help detect autism in the first six months. Ideally, such measures will not rely upon emerging linguistic abilities or complex social behaviors. In a recent study in *Current Biology,* Rozenkrantz and colleagues [3] now describe a possible marker, based on link between olfaction and ASD.

Intriguingly, another core aspect of ASD are altered sensory and motor behaviors. For example, children with ASD may exhibit indifference to pain or temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects or visual fascination with lights or movement. Of central importance in the quest for early diagnosis is the fact that these alterations in sensory and motor behaviors are the earliest behavioral indications of ASD [4]. Measurement of these behaviors may therefore provide a window into early diagnosis.

The olfactory system is a particularly well-suited candidate for assessing sensory and affective behavior in very young children. A unique aspect of olfaction is its relative separation from linguistic processing [5,6]. Aromas are notoriously difficult to identify and name [7]. Think of trying to name a spice in a

dish you are served. You readily detect and recognize the aroma as a favorite flavor, but try as you might, it's identity remains illusive. This is backed by a substantial literature suggesting that the olfactory system is optimized to influence behavior at a 'pre-linguistic' level.

To begin with, the anatomical connections between the olfactory system and the language network are minimal at best [6]. For example, in stark contrast to the visual system, where information about objects is relayed directly to the language network [8], 'olfactory objects' are relayed to regions of the brain critical for memory, emotion and social interaction [5,6]. Thus, olfactory information has a 'fast track' to limbic networks regulating affect and emotion, but poor access to regions of the brain subserving language.

This brain organization is reflected in function. At the same time that odors are difficult to identify and name, they provide important information about the valence of external stimuli that unconsciously shape our opinions and attitudes. For example, unsensed odors experienced in tandem with human faces influence whether or not the face is liked or disliked [9]. Chemosignals sensed in tears [10] and handshakes [11] inform our attraction towards others. Thus, odors play an important role in social communication. Indeed, Yeshurun and Sobel [5] have argued that the primary role of olfaction is hedonic judgment, which occurs independently of odor identification.

Herein lies an opportunity. Innate olfactory behaviors may provide a link between early emerging sensory motor behaviors and the social deficits that characterize ASD. Moreover, this could be achieved independently from language function and thus provide a valid measure at the earliest stages of development. It is this idea that is cleverly exploited by Rozenkrantz and colleagues [3].

The team measured an olfactory behavior called the 'sniff-response', which refers to the characteristic low-magnitude sniffs that occur in response to unpleasant and intense odors versus the high-magnitude sniffs that occur in response to pleasant and mild odors [12]. The sniff-response is an automatic coordinated sensory-motor interplay that is mediated by the same cerebellar circuit that is altered in ASD [12,13]. Key is the fact that it is not dependent on language, training or task and is therefore perfect for use with pre-verbal children.

Figure 1. Autism in a whiff.
A typically developing two-year old girl wearing the custom made set-up of Rozenkrantz and colleagues [3], with which pleasant and unpleasant odors were presented to the children (red line) while their nasal airflow was monitored (green line). (Photo: Ofer Perl.)

The authors designed a pediatric olfactometer that would allow the investigators to simultaneously deliver odors and measure nasal airflow (Figure 1). Using this device they then delivered two pairs of odorants — pleasant and unpleasant — to ASD children and their typically developing peers.

As predicted, the typically developing children altered their sniff to account for odor valence much in the same way as adults. They produce larger sniffs for the pleasant odors and smaller sniffs for the unpleasant odors. In contrast, when considered as a group, the effect was largely absent in the ASD children, who produced equivalent sniffs in response to pleasant and unpleasant odors. More critically, at the individual level they found that the severity of disruption of sniff-response was closely associated with the severity of social, but not motor impairment — an effect unlikely related to simple perceptual alterations since the typically developing and ASD children rated the odors as similarly pleasant.

Next, the authors attempted to classify children as ASD or typically developing. They identified a classifier that relied on sniff volume and duration, which was used to differentiate participants using a leave-one-out analysis. The classifier was 81% accurate, correctly identifying 17 out of 18 typically developing children and 12 out of 18 ASD.

This set of findings is a very exciting new lead towards developing a novel biomarker of ASD that could be utilized even in newborn infants. The measurement technique appears to be ideal, in that it could be performed without the need for instruction, is independent of overt attention, and perhaps, could even be performed while infants and children are asleep. The promise is that — much like the newborn hearing screens — the sniff-response could become a routine screening measure in the standard of care in modern newborn nurseries throughout the world.

The novel measure may also have a second use. It allows access to the fundamental ''disturbances of affective contact'' that have been central to theories of autism since it's initial description [14] and may therefore advance our understanding of emotional dysregulation. Children with ASD exhibit deficits in the perception, understanding and regulation of emotion. Clinical impressions suggest that problems with emotion regulation in ASD can

manifest in ways traditionally seen in children with anxiety and mood disorders, but may also manifest as 'meltdowns', characterized by short-term increases in repetitive behaviors, aggression, self-injurious behavior, withdrawal or general deterioration of functioning. Irrespective of the mode of manifestation, emotional dysregulation has an enormous negative impact on quality of life and exacerbation of social deficits for children with ASD. Despite this, the underlying neurobiological mechanisms have yet to be explored. The measure developed by Rozenkrantz and colleagues [3] promises to provide a nonverbal assessment that will enable testing of an innate form of emotion regulation in even the youngest, most intellectually delayed, minimally verbal children with ASD.

While this is an incredibly exciting development, there are a couple of important caveats: first, we need to know whether this disruption is specific to ASD. For example, we would ultimately want to show that this approach differentiates in the prediction of two very different neurodevelopmental disorders (e.g., ASD vs. schizophrenia). Second, Rozenkrantz and colleagues [3] did not match the ASD and typically developing groups on intellectual ability. As such, the effects may well represent a signature of the intellectual disability that affects roughly 70% of people with ASD.

These caveats notwithstanding, this work represents an important new lead in the field of ASD. The approach bypasses language to provide a non-verbal, non-task dependent assessment of sensory-motor integration and affective response, both of which are postulated to be critical features of ASD. It should generate tremendous excitement and, most importantly, new directions for research.

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